REMARKS

In response to the Office Action dated October 25, 2002, claim 25 has been amended. No new matter has been added. Reconsideration of the claims is respectfully requested.

I. Rejection under the judicially created doctrine of obviousness-type double patenting

On page 2 of the Office Action, claims 1, 2, 4-6, 9-11, 14, and 21-29 were rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over the claims of copending Application No. 09/186810.

Applicants submit that the claims of the present application are distinct and independently patentable from the claims of copending Application Number 09/186810. Reconsideration is respectfully requested. Additionally, Applicants will consider filing a terminal disclaimer complying with 37 CFR 3.73(b) when these claims are allowed.

II. Rejection under 35 U.S.C. § 112

1. On page 3 of the Office Action, claims 25-28 are rejected under 35 U.S.C. § 112 first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants respectfully traverse this rejection, but have amended the application to overcome the objections. Claim 25 has been amended to delete the term "fully" as 'fully" is redundant in that "crosslinked" is different from "partially or lightly crosslinked". It is believed that all claims comply with 35 U.S.C.§ 112 first paragraph.

2. On page 3 of the Office Action, claims 25-28 are rejected under 35 U.S.C. § 112 second paragraph for being indefinite. The Applicants respectfully traverse this rejection. With respect to "exogenous," the dictionary definition of the term, as provided with the previous response, is completely clear in context. The Examiner has failed to state a case for prima facie indefiniteness. Claim 25 has been amended to delete the term "fully", as 'fully" is redundant in that "crosslinked" is different from "partially or lightly crosslinked". It is believed that all claims comply with 35 U.S.C. § 112 second paragraph.

III. Rejection based on under 35 U.S.C. §102(b)/103(a)

1. On page 4 of the Office Action, claims 25 and 28 are rejected under 35 U.S.C. §102(b) as being anticipated by or, alternatively, under 35 U.S.C. §103(a) as being unpatentable over Cahalan, et al. (US 5,308,641).

The Examiner cited the Cahalan patent for disclosing that human or animal tissue is used as the solid surface and the biomolecule is one of the growth factors. See col. 6, lines 14-18; the abstract; col. 4, lines 20-43; and col. 6, lines 8-28. Further, the Examiner noted that light crosslinking might be "fully crosslinking" to the extent defined and described in the Cahalan specification. Applicants maintain that Applicants' invention is not disclosed by the Cahalan patent, and thus the Cahalan patent does not render Applicants' invention prima facie anticipated or obvious.

Cahalan, et al. teaches the use of an improved spacer material and a method for making it, comprising an aminated substrate, a polyalkylimine covalently attached to the aminated substrate and a crosslinking agent. See col. 3, lines 1-20. The crosslinking agent is for crosslinking the polyalkylimine to an aminated substrate. See col. 3, lines 21-34. The polyalkylimine and crosslinking agent together form the spacer used for improving the biocompatability of the substrate to enable the attachment of any biologically active compound to the substrate through the spacer. See col. 4, lines 14-19. Cahalan, et al. further stresses that the spacer material intervenes between the substrate and the biologically active compound, and sometimes, a second spacer is used. See col. 4, lines 58-60, and col. 5, lines 44-55. It also specifically teaches controlled light crosslinking of the polyalkylimine itself to prevent the biomolecule from being buried in the spacer and losing bioactivity and also light crosslinking in the interface between the polyalkylimine and the biomolecule to attach the biomolecule to the polyalkylimine. See col. 3, lines 2-20.

On the other hand, claim 25 teaches a crosslinked tissue having an exogenous polypeptide growth factor associated with it. The crosslinking agent crosslinks the tissue with the growth factor. Applicants submit that the "crosslinked tissue" of claim 25 is different from the "lightly crosslinked" polyalkylimine in Cahalan, et al. First, the term "crosslinked" is different from "partially crosslinked or lightly crosslinked". It denotes

more complete crosslinking than either "partially or lightly". Second, Cahalan, et al. specifies "lightly crosslinked" for achieving its objective of "lightly crosslinking" the polyalkylimine to the substrate on the one hand, and at the same time, "lightly crosslinking" the "lightly crosslinked" polyalkylimine to the biomolecule. Otherwise, the objective of crosslinking the polyalkylimine to both the substrate and the biomolecule will either be defeated, or Cahalan, et al. will have no need to clarify crosslinked with "lightly". See col. 3, lines 2-20.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, all claim elements, and their limitations, must be found in the prior art reference to maintain a rejection based on 35 U.S.C. §102. Applicants respectfully submit that Cahalan, et al. does not teach every element of claim 25, and therefore fails to anticipate claim 25.

Dependent claim 28, dependent from independent claim 25, was also rejected under 35 U.S.C. §102(b) as being unpatentable over Cahalan, et al. While Applicants do not acquiesce with the particular rejections to claim 28, it is believed that this rejection is moot in view of the remarks made in connection with independent claim 25. Claim 28 includes all of the limitations of claim 25, and recites additional features which further distinguish it from the cited reference. Therefore, claim 28 is also in condition for allowance.

Furthermore, the Examiner asserts that "light crosslinking" is only a preferred embodiment in the Cahalan patent and that it would be obvious to proceed to fully crosslinking the polyalkylimine. Applicants respectfully disagree. As noted above, "light crosslinking" is described as an aspect of reaching the objective of linking a biomolecule to the polyalkylamine which is already lightly crosslinked to the support. See, for example, abstract, column 3, lines 13-20, column 4, lines 66 to column 5, line 3; column 7, lines 45-50 Example 5. Light crosslinking of the polyalkylimine ties up some of the polyalkylimine sites via the aldehyde functionality of the crosslinking agent, but not all

of the sites, so that some imine groups are available to bond the biomolecule to the polyalkylimine.

Also, even though Cahalan, et al teaches lightly crosslinked polyalkylimines, the Cahalan patent does not teach, suggest, or motivate "crosslinked tissue". Specifically with respect to lack of motivation, the objectives in the Cahalan patent are completely unrelated to the modification of material properties that would generally result from crosslinking.

Three criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference, or combination of references, must teach or suggest all the claim limitations. MPEP § 2142. Applicants respectfully traverse the rejection since the Cahalan patent does not teach, suggest or motivate Applicants' claimed invention. The Cahalan patent does not render Applicants' claimed invention obvious. Applicants respectfully request withdrawal of the rejection of claims 25 and 28 under 35 U.S.C. §102(b) as anticipated or, alternatively, under 35 U.S.C. §103(a) as being unpatentable over the Cahalan patent.

2. On page 5 of the Office Action, claims 25 and 26 are rejected under 35 U.S.C. §102(b) as being anticipated by or, alternatively, under 35 U.S.C. §103(a) as being unpatentable over Bayne, et al. (EP 0 476 983). The Examiner rejected claims 25 and 26 under 35 U.S.C. §102(b) as being anticipated by the Bayne, et al. European Patent application 0476983 (the Bayne EP application). The Examiner asserts that the Bayne EP application discloses applying fibrin coating, prior to or in addition to the VEGF II coating, onto the surface of the fixed umbilical vein, since the tubular supports include fixed umbilical vein. Applicants continue to believe that this is a misunderstanding of the Bayne EP application. Applicants respectfully request reconsideration.

Bayne, et al. noted that after an adequate number of endothelial cells are grown, these cells are plated on the inside surface of the fixed umbilical vein. See page 8, lines 14-19. No mention is made of prior coating of the umbilical vein with VEGF II or a

protein like fibrin. Bayne, et al. further states that "Following implantation endothelial cells...grow on the **artificial surface**. Prior coating...with proteins such as fibrin...enhance attachment of the cells to the **artificial surface**." (emphasis added) (page 8, lines 17-23). The Bayne EP application does not disclose application of a growth factor to a fixed tissue. Rather, it discloses the application of cells to the tissue.

On the other hand, claim 25 discloses a crosslinked tissue having an exogenous polypeptide growth factor associated with it. Since the Bayne EP application does not disclose every element of the claimed invention, the Bayne EP application does not anticipate claim 25. Claim 26 depends from claim 25 and therefore incorporates all the limitations of claim 25 and is also not anticipated by Bayne, et al. Applicants respectfully request the withdrawal of the rejection of claims 25 and 26 under 35 U.S.C. §102(b) as being anticipated by the Bayne EP application.

The Examiner alternatively rejected claims 25 and 26 as unpatentable under 35 U.S.C. §103(a) over the Bayne EP application. The Examiner asserts that if the tubular supports coated with VEGF II do not include umbilical vein, then it would have been obvious to use umbilical vein as the tubular support. Applicants respectfully traverse the rejection.

Bayne, et al. discloses the application of cells to the tissue. It does not teach the association of crosslinked tissue with a polypeptide growth factor, in particular with VEGF. In addition, it teaches the association of VEGF II with an **artificial surface.** See page 8, lines 20-23. When referring to a fixed umbilical vein, no mention is made of prior coating of the umbilical vein with VEGF II or a protein like fibrin, as noted before. Therefore, Bayne et al does not teach, suggest or motivate application of VEGF with a crosslinked tissue, which is not an artificial surface. Thus, Bayne, et al. does not render claim 25 obvious. Since claim 26 is dependent from claim 25 and incorporates all the limitations of claim 25, it is also not rendered obvious by Bayne, et al. Applicants respectfully request that the rejection of claims 25 and 26 under 35 U.S.C. §103(a) be withdrawn.

3. On page 5 of the Office Action, claims 1-2, 4-5, 9-11, and 29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bayne, et al. in view of Wadström

(US 5,631,011). The Examiner asserts that Bayne, et al. discloses a fixed tissue coated with a fibrin coating (biologic adhesive) that is applied prior to the application of a polypeptide growth factor, VEGF, and that Wadström discloses fibrin as a common biologic tissue adhesive. The Examiner asserts that it would have been obvious to use an allograft or xenograft tissue for the umbilical vein disclosed in the Bayne EP application.

Applicants respectfully traverse the rejection.

Bayne, et al. does not disclose a polypeptide growth factor or protein such as fibrin associated with the umbilical vein, as discussed above. Instead, Bayne, et al. teaches the association of VEGF II with an **artificial surface.** See page 8, lines 20-23. When referring to a fixed umbilical vein, no mention is made of prior coating of the umbilical vein with VEGF II or a protein like fibrin. This deficiency is not supplied by Wadström, as it does not teach, suggest or motivate association of a polypeptide growth factor with tissue. Wadström only teaches an improved fibrin glue without a low viscosity problem and which promotes wound healing without scar formation or development of adhesions. See col. 2, line 65 to col. 3, line 47. Since Wadström is directed to an anti-adherence composition, there is no motivation to combine the teaching of Bayne, et al. with that of Wadström, and the combined teachings do not teach, suggest or motivate the association of polypeptide growth factor with tissue. Therefore, it would not be obvious to associate a polypeptide growth factor with allograft or xenograft tissue.

In addition, Wadström does not disclose the use of a biologic adhesive to associate a growth factor with a material, as it is mainly concerned with an anti-adherence composition. Though fibrin is a polymer, it is not an adhesive. A mixture of fibrinogen and thrombin is an adhesive, which can be called a fibrin adhesive since fibrin is formed in the reaction. See col. 1, lines 17-28. Once fibrin is formed, the adhesive properties are no longer present since the fibrin protein itself is not adhesive. See also col.1, lines 17-28. Since Bayne, et al. does not teach, suggest or motivate the use of an adhesive to associate a growth factor with a substrate, the combined disclosures of Bayne, et al. and ö do not teach, suggest or motivate association of a polypeptide growth factor with a substrate using an adhesive, the subject matter of claims 1 and 29.

Claims 2, 4-5, and 9-11 are dependent from claim1. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 1. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Therefore, dependent claims 2, 4-5 and 9-11 are also in condition for allowance. Applicants respectfully request the withdrawal of the rejection of claims 1-2, 4-5, 9-11, and 29 as being unpatentable over Bayne, et al., in view of Wadström.

4. On page 6 of the Office Action, claims 6-8, 14, 15, 21-24, and 27-28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bayne, et al. and Wadström and further in view of Carpentier, et al. (US 4,648,881). The Examiner cited Carpentier, et al. for disclosing uncrosslinked and crosslinked tissue, heart valve tissue and other types of tissue. The Examiner asserted that it would have been obvious to use these materials as the substrates within the teaching of Bayne, et al. for the application contemplated by Carpentier.

Applicants respectfully traverse the rejection.

Bayne, et al. does not disclose the tissue, such as fixed umbilical vein, with the growth factor or an adhesive or specific binding interactions to associate a protein with a substrate. This deficiency is not supplied either by Wadström or Carpentier, et al . As noted above, Wadström is more directed to an anti-adherence composition, and does not teach or suggest the use of a biologic adhesive for association of active biomolecules with a substrate. Carpentier, et al. discloses treatments of tissue to reduce the incidence of calcification and does not disclose the association of biologically active proteins with tissue. Thus, there would have been no motivation to combine the teachings of these references. In addition, the combined references do not teach, suggest or motivate association of growth factors with valved protheses or the association of biologically active molecules with a substrate using a biological adhesive. Therefore, the combination of the references does not render claims 6-8, 14, 15, 21-24, and 27-28 obvious.

In view of the above comments, Applicants respectfully request withdrawal of the rejection of claims 6-8, 14, 15, 21-24, 27 and 28 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application and the Wadström patent as applied to claims 1-5, 9-11 and 29, and further in view of the Carpentier patent.

In view of the amendments and reasons provided above, it is believed that all pending claims are in condition for allowance. Applicants respectfully request favorable reconsideration and early allowance of all pending claims.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' attorney of record, Hallie A. Finucane at 952-253-4134.

Respectfully submitted,

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Appendix A
Marked Up Version of the Entire Claim Set

The entire set of pending claims is provided for the Examiner's convenience.

1. (Unchanged) A prosthesis for a human patient comprising allograft or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive, antibody-antigen associations, specific binding protein-receptor associations or enzyme substrate associations, said polypeptide growth factor being effective to stimulate the affiliation of viable cells with said tissue.

2. (Unchanged) The prosthesis of claim 1 wherein said binding of said polypeptide growth factor to said tissue involves specific binding interactions.

4. (Unchanged) The prosthesis of claim 1 wherein said binding of said polypeptide growth factor to said tissue involves a linker molecule.

5. (Unchanged) The prosthesis of claim 1 wherein said tissue comprises crosslinked tissue.

6. (Unchanged) The prosthesis of claim 1 wherein said tissue comprises uncrosslinked tissue.

7. (Unchanged) The prosthesis of claim 1 wherein said tissue comprises a porcine heart valve.

8. (Unchanged) The prosthesis of claim 1 wherein said tissue comprises bovine pericardial tissue.

9. (Unchanged) The prosthesis of claim 1 wherein said polypeptide growth factor comprises vascular endothelial growth factor.

10. (Unchanged) The prosthesis of claim 9 wherein said vascular endothelial growth factor comprises a protein selected from the group consisting of bVEGF164, bVEGF120, hVEGF165, hVEGF121, VEGF II, hVEGF80, VEGF-B, VEGF2, modified active forms thereof, and combinations thereof.

11. (Unchanged) The prosthesis of claim 1 wherein said tissue comprises synthetic tissue.

14. (Unchanged) A prosthetic heart valve comprising a substrate with associated VEGF, wherein said VEGF is associated with the substrate by direct attachment, a biologic adhesive, covalent bonding using crosslinking agents, antibody-antigen associations, specific binding protein-receptor associations or enzyme-substrate associations, the prosthesis having a valve structure, said polypeptide growth factors being effective to stimulate the affiliation of viable cells with said substrate.

15. (Unchanged) The prosthetic heart valve of claim 14 wherein said prosthetic heart valve comprises a porcine heart valve.

21. (Unchanged) The prosthetic heart valve of claim 14 wherein the substrate comprises tissue.

22. (Unchanged) The prosthetic heart valve of claim 21 wherein said tissue comprises uncrosslinked tissue.

23. (Unchanged) The prosthetic heart valve of claim 21 wherein said tissue comprises crosslinked tissue.

24. (Unchanged) The prosthetic heart valve of claim 14 wherein the substrate comprises a synthetic polymer.

25. (Amended) A prosthesis comprising [fully] crosslinked tissue having an exogenous polypeptide growth factor associated therewith.

26. (Unchanged) The prosthesis of claim 25 wherein said polypeptide growth factor comprises vascular endothelial growth factor.

27. (Unchanged) The prosthesis of claim 25 wherein said crosslinked tissue comprises a crosslinked heart valve.

28. (Unchanged) The prosthesis of claim 25 wherein said crosslinking involves glutaraldehyde moieties.

29. (Unchanged) A prosthesis for a human patient comprising allograft or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive, covalent bonding using crosslinking agents comprising reactive functional groups, antibody-antigen associations, specific binding protein-receptor associations or enzyme substrate associations, said polypeptide growth factors being effective to stimulate the affiliation of viable cells with said tissue.